The new ASAS classification criteria for axial and peripheral spondyloarthritis: promises and pitfalls

Spondyloarthritis (SpA), if not diagnosed and treated early, often leads to significant morbidity. Unfortunately, diagnosis and implementation of therapy are frequently delayed, in many cases by years. The Assessment of SpondyloArthritis International Society has recently developed new criteria for classification of both axial and peripheral SpA. The new criteria were formulated with the aim of enhancing design of clinical trials, and ultimately leading to earlier and more effective diagnosis and treatment in the clinical setting. This paper reviews the process of the development of both sets of criteria, and discusses their potential advantages and disadvantages.

KEYWORDS: ankylosing spondylitis axial spondyloarthritis dactylitis enthesitis HLA-B27 inflammatory bowel disease-related arthritis psoriatic arthritis reactive arthritis sacroiliitis spondylitis

Spondyloarthritis (SpA) is an umbrella term applied to a group of rheumatic diseases with features in common with and distinct from other inflammatory arthritides, particularly rheumatoid arthritis. SpA encompasses ankylosing spondylitis (AS), reactive arthritis, psoriatic arthritis, inflammatory bowel disease-related arthritis and undifferentiated SpA. Features that link these entities are an association with HLA-B27, a characteristic pattern of peripheral arthritis that is asymmetric, oligoarticular and predominates in the lower extremities, and possible sacroiliitis, spondylitis, enthesitis, dactylitis and inflammatory eye disease [1]. Estimated prevalence of ankylosing spondylitis in Europe is 0.3-0.5%, and of SpA is 1-2%, which is higher than rheumatoid arthritis [2]. Data from National Health and Nutrition Examination Survey (NHANES) suggest that prevalence of SpA in the USA may be as high as 1.4% [3].

AS, with typical onset at a young age, without treatment or with delayed treatment, is associated with tremendous symptomatic burden and loss of function during years that are normally productive [4]. Opportunities for early treatment are hampered by delayed diagnosis; an average delay of 8–11 years between onset of symptoms and time of diagnosis has been reported [5]. Reasons for the delay in diagnosis are myriad and include lack of a pathognomonic clinical feature or laboratory test. Low back pain afflicts most patients with AS, but is extremely common in the general population, and often the inflammatory origins of back pain are not carefully sought in practice [4]. Furthermore, radiographic sacroiliitis, which has historically been a cornerstone of diagnosing AS, may take several years to develop [6].

The need for early diagnosis and treatment was less crucial in the past, when therapeutic options were quite limited. This has changed with the development of TNF- α inhibitors that are used effectively to treat AS and arrest progression of peripheral arthritis in other SpA [7]. A major challenge over recent decades has been the lack of diagnostic or classification criteria, which could help with early establishment of diagnosis to allow for timely and proper treatment, and facilitate clinical trial design, respectively. The development of the Assessment of SpondyloArthritis International Society (ASAS) classification criteria for both axial and peripheral SpA has been a welcome advance in this regard. This article discusses the new criteria and their potential promises and pitfalls.

Evolution of the new criteria

As mentioned earlier, one of the challenges in diagnosing AS is that low back pain, its cardinal clinical symptom, is extremely common in the general population. According to recent NHANES data, chronic low back pain is seen in 19% of Americans [3]. The modified New York criteria for classification of AS were developed in 1984 [8]. They required fulfillment of at least one clinical criterion plus presence of radiographic sacroiliitis. While the inclusion of inflammatory back pain (IBP) as a clinical criterion replaced the less specific symptom of low back pain that had been used in the Rome and prior New York criteria, reliance on radiographic sacroiliitis left the remaining problem of lack of sensitivity when

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ISSN 1758-4272

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Figure 1. European Spondyloarthropathy Study Group criteria. SpA: Spondyloarthritis.

applied to patients early in their disease course [9]. The Amor and European Spondyloarthropathy Study Group (ESSG) criteria (FIGURE 1 & TABLE 1) were developed in the 1990s [10,11].

While the modified New York criteria solely addressed classification of AS, the Amor and the ESSG criteria addressed the entire spectrum of SpA, including undifferentiated disease, which had previously been ignored in many studies owing to lack of a workable definition. The ESSG criteria have 'entry conditions' in that they require the presence of inflammatory spinal pain or synovitis. The Amor criteria are a list of twelve variables, with no mandatory features required for classification. The Amor criteria perform slightly better than ESSG in classification of early SpA, which may be attributable to the Amor inclusion of response to NSAIDs and *HLA-B27* typing [12].

The new ASAS classification criteria for axial SpA

Development of the new criteria (see FIGURE 2) began with 20 experts in SpA (all ASAS members) reviewing clinical data of 71 real patients who had presented to a rheumatology department in Berlin (Germany). The patients were selected based on a history of chronic back pain of unknown origin and a possible diagnosis of SpA. Clinical data included gender, age, duration of back pain, clinical history, laboratory tests and imaging results, and were presented to the experts in the format of 'paper patients'. In terms of imaging, information about sacroiliitis on plain radiographs was provided according to the modified New York criteria. Additionally, all patients underwent sacroiliac joint MRI, and MRI findings were conveyed as presence or absence of active inflammation [13].

Paper patients were first presented and classified without MRI information and candidate criteria were formulated based on clinical reasoning, including review of imaging data. One of the interesting findings during the process of developing candidate criteria was the large proportion of patients (96%) who lacked definite radiographic sacroiliitis and were hence considered to have nonradiographic axial SpA. In addition, MRI was found to play a substantial role in classification. In 21% of patients, the experts' classification changed once MRI information was presented. It was also felt that the new criteria

Table 1. Spondyloarthropathies Amor Criteria 1990.	
Clinical characteristic	Score
Lumbar pain at night or lumbar morning stiffness	1
Asymmetric oligoarthritis	2
Buttock pain (or bilateral alternating buttock pain)	1 (2)
Sausage-like toe or digit(s)	2
Heel pain or other well-defined enthesities	2
Iritis	2
Nongonococcal urethritis/cervicitis within 1 month of onset	1
Acute diarrhea within 1 month of arthritis onset	1
Psoriasis, balanitis or inflammatory bowel disease (Crohn's or ulcerative colitis)	2
Sacroiliitis (bilateral grade 2 or unilateral grade 3)	2
HLA-B27(+) or (+) family history of a spondyloarthropathy	2
Rapid (<48 h) response to NSAIDs	2
Diagnosis of a spondyloarthropathy requires a score of ≥ 6 . Data taken with permission from [11].	

Int. J. Clin. Rheumatol. (2012) 7(6)

should allow for classification based on clinical criteria alone, and the number and combination of clinical features were selected based on a balance of sensitivity and specificity. Sets of candidate criteria were comprised mainly of positive imaging plus one clinical feature, or IBP plus two clinical features [13].

The candidate criteria were then validated in an independent prospective international study of 649 patients from 25 centers. Inclusion requirements were a history of chronic back pain (at least 3 months duration) of unknown etiology that began before 45 years of age, with or without peripheral symptoms. In an effort to prevent selection bias, patients were enrolled in a strictly consecutive matter. In addition to history, physical examination and laboratory testing that included HLA-B27 and CRP, patients underwent plain radiographs of the pelvis. Sacroiliitis was graded for each sacroiliac joint separately (grades 0-4). MRI of the sacroiliac joints was required in the first 20 patients in each center, while MRI of the spine was optional. MRI findings were recorded as the presence or absence of active inflammation, omitting chronic changes such as erosions and fatty degeneration [14].

Diagnosis by an expert physician (axial SpA or no SpA) was used as the gold standard. Following data analysis and presentation, the final criteria were determined by vote of ASAS members. The final criteria include an imaging arm and a clinical arm: by applying the final criteria, a patient with chronic back pain of onset at before the age of 45 years can be classified as having axial SpA if there is sacroiliitis on imaging (by radiographs or MRI) along with at least one other SpA feature, or if imaging evidence of sacroiliitis is absent, positive HLA-B27 along with at least two other SpA features [14]. The new criteria performed well in the validation study. Sensitivity was 82.9% and specificity was 84.4%. The new criteria also outperformed the ESSG and Amor criteria, even after incorporating 'sacroiliitis on MRI' into the earlier criteria [15].

Promises & pitfalls of the new axial SpA criteria

One of the notable aspects of these criteria is the incorporation of the emerging concept of 'nonradiographic' axial SpA. This refers to patients with signs and symptoms of axial disease who lack the radiographic damage to the sacroiliac joints to meet the modified New York criteria [16]. This entity may be part of the same spectrum of disease as AS (see Figure 3). Investigators of the German Spondyloarthritis Inception Cohort (GESPIC)



Figure 2. Axial spondyloarthritis classification criteria.

[†]Active (acute) inflammation on MRI, highly suggestive of sacroiliitis associated with SpA or definite radiographic sacroiliitis according to the modified New York criteria. [†]Inflammatory back pain, arthiritis, enthesitis (head), uveitis, dactylitis, psoriasis, Crohn's disease (ulcerative colitis), good response to NSAIDs, family history of SpA, *HLA-B27* and elevated CRP. SpA: Spondyloarthritis.

Data taken with permission from [14].

sought to prospectively study the disease course of patients with early axial SpA and identify predictors of outcome. They compared patients with established early AS and patients with nonradiographic SpA (the latter diagnosis had to be determined by the treating rheumatologist, and was carried out prior to the publication of the new criteria). Clinical manifestations, presence of *HLA-B27* and levels of disease activity were found to be quite similar between the groups [17].

The inclusion of MRI, given equal weight as radiographic sacroiliitis, in the criteria is a crucial advancement. Advantages of MRI include multiplanar imaging, absence of ionizing radiation and superior tissue contrast resolution [18]. MRI is highly sensitive for detection of sacroiliitis, mainly via demonstration of bone marrow edema representing early stages of inflammation. This is usually best seen on fat suppressed T2-weighted or short tau inversion recovery (STIR) sequences, by which increased water content (representing cellular infiltration or replacement of bone marrow fat) heightens signal intensity. Alternative techniques requiring contrast agents include fat-suppressed T1-weighted images following the gadolinium administration, with heightened signal intensity representing changes in tissue perfusion. Potential disadvantages of contrast administration, however, include cost, requirement of intravenous access and potential risk of nephrogenic systemic fibrosis [16]. The ability to detect sacroiliitis by MRI during early stages of disease, well before detection by radiographs is possible, has been demonstrated [19]. Furthermore, one study demonstrated the utility of bone marrow edema surrounding the sacroiliac joints on MRI in predicting subsequent development of AS [20].

The definition of a positive MRI, or 'active sacroiliitis by MRI', applied in the new criteria was determined by consensus by rheumatologists and



Figure 3. Spectrum from spondyloarthritis to ankylosing spondylitis. Data taken with permission from [9]. SpA: Spondyloarthritis.

> radiologists comprising the ASAS/OMERACT trials MRI working group. Among the active inflammatory lesions detectable by MRI, the clear presence of either bone marrow edema on STIR or osteitis on T1 postgadolinium imaging was deemed a requirement in defining active sacroiliitis. The presence of structural lesions (such as fat deposition, sclerosis, erosions and bony ankylosis), while likely to reflect previous inflammation, were not felt to sufficiently define a positive MRI in the absence of bone marrow edema or osteitis [21]. The superior sensitivity of MRI was supported in the evaluation of the ASAS 'paper patients'. Only 2.8% of patients had definite sacroiliitis according to the modified New York criteria, but 38% of them were found to have sacroiliitis on MRI [13]. It should be noted, however, that bone marrow edema of the sacroiliac joints is not perfectly specific for inflammation, as it can be present in other settings that include mechanical stress [21]. Thus, inappropriate use of the sacroiliac joint MRI in a young patients with chronic back pain of mechanical origin has a danger of misdiagnosis. Another potential limitation of the criteria is the exclusion of spinal MRI, which could have improved sensitivity as well as specificity [20].

> Ability to classify someone with nonradiographic axial SpA, even in the absence of positive MRI, using the 'clinical arm' (i.e., positive *HLA-B27* with at least two SpA features) is one of the advantages of the new axial SpA criteria. However, since the prevalence of *HLA-B27* amongst white Caucasians within the USA is known to be 7.5%, some people could get misclassified if they have soft signs/symptoms of SpA along with positive *HLA-B27* by chance. This misclassification would increase if the person comes from an ethnic group that has an even higher prevalence of *HLA-B27* (such as some Native American populations). This pitfall should be kept in mind when classifying people using the 'clinical arm' of the criteria.

The axial SpA criteria and definition of a positive MRI were studied in an inception cohort comparing patients with IBP to control patients. All of the patients with IBP were classified as having axial SpA, with more patients meeting the imaging arm of the criteria than the HLA-B27 arm (83 vs 62%, respectively). Both arms showed good diagnostic utility but were less valuable for prediction of radiographic progression. This might be due to limited specificity of the ASAS definition of a positive MRI at baseline, or it may be that MRI evidence of sacroiliitis may not truly be a good prognostic marker. Prognostic utility may also be limited by inclusion of mild bone marrow edema in the definition of a positive MRI, and a role for additional prognostic factors independent of MRI findings [22].

As discussed above, the disease burden of nonradiographic SpA is quite similar to that of AS. It is, therefore, imperative to establish a mode of early and effective diagnosis and treatment of this entity. The new criteria are expected to enhance design of future clinical trials and observational studies [23]. This may have direct therapeutic implications, supported by evidence of efficacy of anti-TNF agents in patients with nonradiographic SpA [24,25]. While designed for classification and not diagnostic purposes, the criteria may have a role in diagnosis in the setting of a rheumatology clinic. When they were applied in this setting to patients with undiagnosed back pain, pretest probability of axial SpA of 60% increased to a post-test probability of 89%, with a positive likelihood ratio of 5.3 [14].

Caution must be exercised, however, in the extrapolation of classification criteria to the clinic. While the diagnostic performance of the new criteria in the outpatient rheumatology clinic was good, it was not perfect. Fulfillment of classification criteria, which work well in the study of groups of patients, does not necessarily translate directly to a diagnosis in an individual patient [26]. As noted above, one other aspect of delay in diagnosis that remains a challenge is facilitating referral to the rheumatologist of appropriate patients with back pain and a high pretest probability of axial SpA. It is not yet clear whether the criteria could have utility in such 'referral clinic' settings, and while this remains unanswered there is risk of misuse of them as diagnostic criteria [15]. This risk is pronounced when classification criteria are applied in a population with a low pretest probability of disease [9] and could lead to inappropriate use of anti-TNF agents to treat patients with chronic mechanical back pain.

The new ASAS classification criteria for peripheral SpA

The process of developing the new criteria for peripheral SpA (see FIGURE 4) was similar to that for axial SpA. Two sets of candidate criteria were formulated based on clinical reasoning and then tested in 35 'paper patients', adjusted and validated. Patients without back pain and with peripheral manifestations that usually began before the age of 45 years, but without an established diagnosis, were included. Two hundred and sixty six patients from 24 centers were recruited. Again, in an effort to minimize selection bias patients were enrolled in a strictly consecutive manner, and again clinical diagnosis (SpA or no SpA) by an ASAS rheumatologist was used as the gold standard. A final set of criteria showing the best balance of sensitivity (77.8%) and specificity (82.9%) was decided upon. It consists of peripheral arthritis (usually lower limb predominant and asymmetric) and/or enthesitis and/or dactylitis) plus additional features. These additional features may include one or more of the following: psoriasis, inflammatory bowel disease, preceding infection, HLA-B27, uveitis and sacroiliitis on imaging. Alternatively, they may include two or more of the following: arthritis, enthesitis, dactylitis, history of previous IBP and family history of SpA [27].

These new criteria, akin to the criteria for axial SpA, performed better than versions of the Amor and ESSG criteria (which were modified to include MRI findings), particularly in terms of sensitivity [27]. Additionally, a combination of the new criteria for axial and peripheral SpA was compared to the modified versions of the Amor and ESSG criteria in the entire ASAS population of 975 patients. The balance of sensitivity and specificity of the combined new criteria was found to be superior to both of the older criteria sets. These figures for the combined new criteria were sensitivity of 79.5% and specificity of 83.3%, compared with 79.1 and 68.8%, respectively for the modified ESSG criteria, and 67.5 and 86.7%, respectively, for the modified Amor criteria [27].

Promises & pitfalls of the new peripheral SpA criteria

The criteria for peripheral SpA call for a reorganization of inter-related diseases into groups based on clinical manifestations rather than underlying individual disease entities (see FIGURE 5). To some experts, referred to as 'lumpers', this is appropriate because they consider different SpA entities as variable expression of the major features of the same disease. Unifying features invoked in support of this approach include association with *HLA-B27*, common ground in therapies employed and potentially shared pathogenic mechanisms. A genetic link is suggested by findings that include a higher frequency of psoriasis in patients with Crohn's disease than in controls [28]. It is hoped that the new criteria will allow for clinical trials to examine diagnostic and therapeutic interventions in a defined clinical subgroup, regardless of the underlying etiology [12].

One of the advantages of the new peripheral criteria is the inclusion of monoarthritis and polyarthritis in addition to oligoarthritis, leading to increased sensitivity of the criteria. Another advantage is that fewer clinical features are required to fulfill the new criteria. A notable distinction between these and the ESSG criteria is that enthesitis and dactylitis are included as entry criteria along with arthritis, so a patient who presents with enthesitis and/or dactylitis but without arthritis could be classified. The addition of *HLA-B27* is also considered an advantage, since all spondyloarthritides share association with this gene [29].

On the other hand, 'splitters' assert that differences between the individual disease entities that can cause peripheral SpA are significant enough to warrant separate consideration in classification criteria. They cite differences in clinical presentation, etiology and genetics that should be recognized. Another concern is that in the setting of a trial it may be challenging to interpret outcome measures that have been validated in one subset of SpA but not others, and treatment responses may be misinterpreted [28]. Emerging data regarding treatment of individual entities may also be overlooked by the criteria and not addressed in clinical trials. One example of this is the recent work supporting combination antibiotics in the management of Chlamydia-induced reactive



Figure 4. Peripheral spondyloarthritis classification criteria. SpA: Spondyloarthritis.

Data taken with permission from [27].



Figure 5. Inter-relationship between the new split of spondyloarthritis according to the Assessment of SpondyloArthritis International Society classification criteria and the present family of disorders. SpA: Spondyloarthritis.

Data taken with permission from [12].

arthritis [30]. Since the CASPAR criteria for the classification of psoriatic arthritis (PsA) already exist, it is unlikely that these new peripheral SpA criteria would be used in clinical trials designed specifically on PsA patients [31].

Another potential drawback is the exclusion of patients with disease initiation after the age of 45 years, which is not uncommon in peripheral SpA. It also remains unclear what degree of spinal involvement should allow for classification of a patient with peripheral involvement, and similarly what degree of peripheral involvement is allowed in classification of axial SpA. One or both sets of criteria may be fulfilled at different points in disease course, and this could hamper the consistency of classification in clinical trials [12]. The same cautions mentioned above regarding misuse of classification criteria, which have been validated in a group of patients, for diagnosis in an individual patient in inappropriate clinical settings (i.e., low pretest probability) also apply.

Conclusion

A major challenge obstructing the effective treatment of SpA has been delay in diagnosis. The new ASAS classification criteria provide promise for incorporation of data into means of improving and streamlining clinical trial design, which will hopefully lead toward earlier diagnosis and initiation of proper therapy for individual patients. The criteria for axial SpA incorporate the concept of nonradiographic axial SpA and a role for MRI in evaluation of SpA. They perform favorably when compared to the older Amor and ESSG criteria. The reorganization of peripheral SpA entities proposed by the new criteria is viewed by some as an advance and by others as detrimental. Advances include the increased emphasis on enthesitis and dactylitis, and the inclusion of *HLA-B27*. The decision to not distinguish between individual entities may cause confusion in the interpretation of outcome measures and treatment responses, and may not include available data on specific entities. Concerns that apply to both sets of criteria include the potential misuse as diagnostic criteria in individual patients with low pretest probability of SpA. Possible overlap and change over time between degrees of axial and peripheral involvement may also pose challenges.

Future perspective

Over the coming years work will likely focus on validating these criteria further and assessing their value in the setting of clinical trials. Goals for future study include further clarifying the entity of nonradiographic axial SpA and defining the role for MRI in the diagnosis, clinical follow-up and evaluating the prognosis of axial SpA. Further study and discussion will also continue surrounding what is the most apt scheme for categorizing the various forms of peripheral SpA, and how much overlap in therapy among the different entities should be considered appropriate. As clinical trial data emerge and outcome measures are analyzed the criteria may require further refinement. Future work will also address the utility of these criteria when translated into various clinical settings and will help address whether they should play a role in diagnosis of individual patients. Overall, despite some concerns and potential limitations, they represent an important step forward in the pursuit of effective methods of early diagnosis and of meaningful clinical research in the area of SpA.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Executive summary

Spondyloarthritis

- Features linking this group of diseases include association with HLA-B27, peripheral arthritis that is typically asymmetric and lower limb predominant, and possibly include sacroiliitis, spondylitis, enthesitis, dactylitis and inflammatory eye disease.
- Diagnosis, and hence the implementation of proper treatment, is often delayed by years.

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Radiographic sacroiliitis, historically the cornerstone of diagnosis, can take years between 5 and 10 years from the start of symptoms to develop.

New features of the Assessment of SpondyloArthritis International Society axial spondyloarthritis criteria

- The concept of nonradiographic axial spondyloarthritis.
- Recognition of a role of MRI in identification of sacroiliitis.

New features of the Assessment of SpondyloArthritis International Society peripheral spondyloarthritis criteria

- Diseases grouped by clinical features rather than by individual disease entities.
- Inclusion of dactylitis and enthesitis as entry criteria.
- Inclusion of monoarthritis and polyarthritis in addition to oligoarthritis.

Conclusion

- While the new criteria represent a step forward in many ways, there are some concerns that remain; further study is required to establish their role in spondyloarthritis classification and diagnosis in an individual patient.
- These criteria appear to perform well when compared with older sets of criteria for spondyloarthritis, and it is hoped that they will be used to enhance the design of clinical trials.
- In most clinical settings, caution must be exercised when attempting to employ classification criteria as diagnostic tools.

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